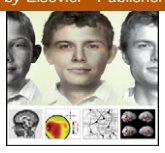
Developmental Cognitive Neuroscience 1 (2011) 600–605

Developmental Cognitive Neuroscience

journal homepage: http://www.elsevier.com/locate/dcn



Individual differences in cocaine conditioned taste aversion are developmentally stable and independent of locomotor effects of cocaine

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ARTICLE INFO

Article history:
Received 2 March 2011
Received in revised form 29 April 2011
Accepted 17 May 2011

Keywords:
Adolescence
Cocaine
Conditioned aversion
Rat
Addiction
Avoidance

ABSTRACT

Drugs of abuse induce complex motivational states in their users which have been shown to vary developmentally. In addition to developmental variation, interindividual variation in the rewarding and aversive effects of drugs of abuse is an important consideration. A rat model was used to assess whether the conditioned rewarding/aversive effects of cocaine were maintained as individuals matured from adolescence into adulthood. We tested rats in the cocaine conditioned taste aversion task as adolescents and again in adulthood. We observed a wide range of approach/avoidance behaviors in this task, and also observed that the relative interindividual differences in approach/avoidance are remarkably stable across the two developmental stages. Furthermore, we observed that these interindividual differences are not attributable to individual differences in cocaine-induced locomotor effects or individual differences in blood or brain cocaine levels. Taken together, these findings indicate that sensitivity to cocaine's motivational effects is stable across development and part of a unique neurological process.

1. Introduction

Drugs of abuse induce a complex pattern of motivational states in their users which can both promote and discourage drug taking. Initial rewarding and aversive effects are predictive of the likelihood of future intake: if a drug makes a user feel good, then the user will likely take it again (Haertzen et al., 1983). If the drug makes the user feel bad, then the user will likely avoid it in the future (Thomas, 1996). After long-term drug taking, withdrawal effects can promote subsequent use: more severe physiological and/or psychological withdrawal is related to greater likelihood of relapse (Koob and Le Moal, 2001). Addiction results from repeated drug taking, therefore any factor that increases motivation to take a drug also increases the likelihood of addiction.

It is well-established that these motivational effects of drugs of abuse vary developmentally. Of particular interest is the comparison of adolescents to adults, because it is well-documented that (1) most experimentation with addictive drugs begins during adolescence (Chen and Kandel, 1995; SAMHSA, 2008) and (2) individuals that initiate drug intake earliest are at the greatest risk of subsequent development of addiction (Brown et al., 2004; DeWit et al., 2000; Lewinsohn et al., 1999; Lynskey et al., 2003; Meyer and Neale, 1992; Patton et al., 2004; Prescott and Kendler, 1999; Robins and Przybeck, 1985). In general, upon drug initiation, the balance between rewarding and aversive effects is tilted towards reward in adolescence (reviewed in Schramm-Sapyta et al., 2009). Furthermore, after long-term drug taking, withdrawal symptoms are reduced in adolescents compared to adults (reviewed in Schramm-Sapyta et al., 2009).

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doi:10.1016/j.dcn.2011.05.004

Several rodent studies demonstrate developmental differences in motivational effects of drugs of abuse. First, adolescents exhibit less conditioned aversion to drugs of abuse than adults (Infurna and Spear, 1979; Philpot et al., 2003; Quinn et al., 2008; Schramm-Sapyta et al., 2007; Schramm-Sapyta et al., 2010; Schramm-Sapyta et al., 2006; Wilmouth and Spear, 2004). Second, adolescents exhibit greater relapse-like ethanol drinking (Schramm-Sapyta et al., 2010). Furthermore, individual differences in sensitivity to aversion during adolescence are predictive of relapse drinking (Schramm-Sapyta et al., 2010). There is thus significant evidence to suggest that adolescent rats are less sensitive to the aversive effects of various drugs than adults, and that differences in aversive experience associated with drug exposure influence the subsequent motivation of the animal to either approach or avoid the drug.

Despite these developmental differences in drug effects, most adolescents who experiment with drugs of abuse do not become addicts. Therefore, individual differences in vulnerability likely interact with developmental stage. We therefore sought to determine whether the most vulnerable individuals maintain a high level of risk throughout life, or whether their risk is reduced with maturation into adulthood. Specifically, we examined whether the relative interindividual differences in the motivational effects of acute drug exposure are consistent throughout life and whether those interindividual differences were explained by pharmacological sensitivity.

Using the conditioned taste aversion task, we observed, first, that interindividual differences in approach vs. avoidance of drug-paired saccharin are maintained from adolescence into adulthood. The animals that approached the drug-paired saccharin during adolescence also approached it in adulthood, and those that avoided it also did so at both developmental stages. Second, we observed that the individual differences in the motivational effects of the drug were not attributable to individual differences in the locomotor effects of cocaine, nor were they directly attributable to individual differences in the levels of the drug in the brain or blood. These findings lead us to conclude that cocaine's motivational effects are conserved throughout development and independent of the other pharmacological effects examined here.

2. Methods

2.1. Conditioned taste aversion

The conditioned taste aversion task consists of a six-day procedure as previously described (Schramm-Sapyta et al., 2006, 2007, 2010). On day 1, rats were water deprived. Twenty-four hours later (day 2), the rats were moved into test cages and where water was available for 20 min. Amount consumed is determined by weighing bottles before and after the drinking session. On day 3, rats were water deprived as on day 1. On day 4, 0.2% saccharin solution was available to the rats for 20 min. At the end of this 20 min period, each rat immediately received an intraperitoneal injection of 10 mg/kg cocaine in saline in a volume of 1 mL/kg. Following the injection, rats were returned to their home cages. On day 5, rats were again water deprived. On day 6 both water and 0.2% saccharin solution were available for 20 min. CTA score is calculated as the amount of saccharin consumed on day 6 divided by the total fluid consumption (both saccharin and water) on day 6.

For experiment 1, this six-day procedure was performed on a group of 12 rats when they were 28–33 days of age (adolescence), and again when they were 88–93 days of age (adulthood). The full procedure (training and testing) was performed at both ages. Linear regression was used to assess the correlation between the CTA scores at the two timepoints.

2.2. Locomotion

In experiment 2, rats ($N = 49$) were tested in CTA at 28–33 days of age as described above. However, on days 2 and 4, rats were placed in locomotor recording chambers immediately following the water drinking session (day 2) and the saccharin drinking session and injection (day 4). Total distance traveled (cm) was recorded for 1 h. Linear regression was used to assess the correlation between locomotor distance traveled and CTA score.

2.3. Pharmacokinetics

A third group of rats ($N = 21$) were tested in CTA at 28–33 days of age as described in experiment 1. One week later, these rats were given a second intraperitoneal injection of 10 mg/kg cocaine and sacrificed 30 min later by decapitation under isoflurane anesthesia. Previous experiments have demonstrated that this time point represents the peak of cocaine levels in the brain after an intraperitoneal injection (Caster et al., 2005). Trunk blood and brain tissue were collected. Brains were frozen immediately on dry ice; blood was centrifuged in the presence of heparin and sodium fluoride for collection of plasma, which was stored at −80 °C. Plasma and brain samples were then sent to the Center for Human Toxicology, University of Utah, where they were analyzed for levels of cocaine and its metabolites by standard methods (Lin et al., 2001, 2003). Linear regression was used to assess the correlation between CTA score and levels of cocaine in brain and blood.

3. Results

3.1. Relative scores in conditioned taste aversion are consistent from adolescence into adulthood

As shown in Fig. 1, cocaine elicited a wide range of CTA scores, from full avoidance of the cocaine-paired saccharin to near-maximal preference of cocaine-paired saccharin. Furthermore, also seen in Fig. 1, there is a high correlation between a rat's CTA score in adolescence and its CTA score in adulthood ($R^2 = 0.93$; $p < 0.0001$). Rats that exhibited a high level of aversion to cocaine in adolescence continued to be highly averse to cocaine as adults, as indicated by their consistently low CTA scores. Conversely, rats with low aversion to cocaine in adolescence remained less averse to cocaine as adults, as reflected by their high CTA scores.

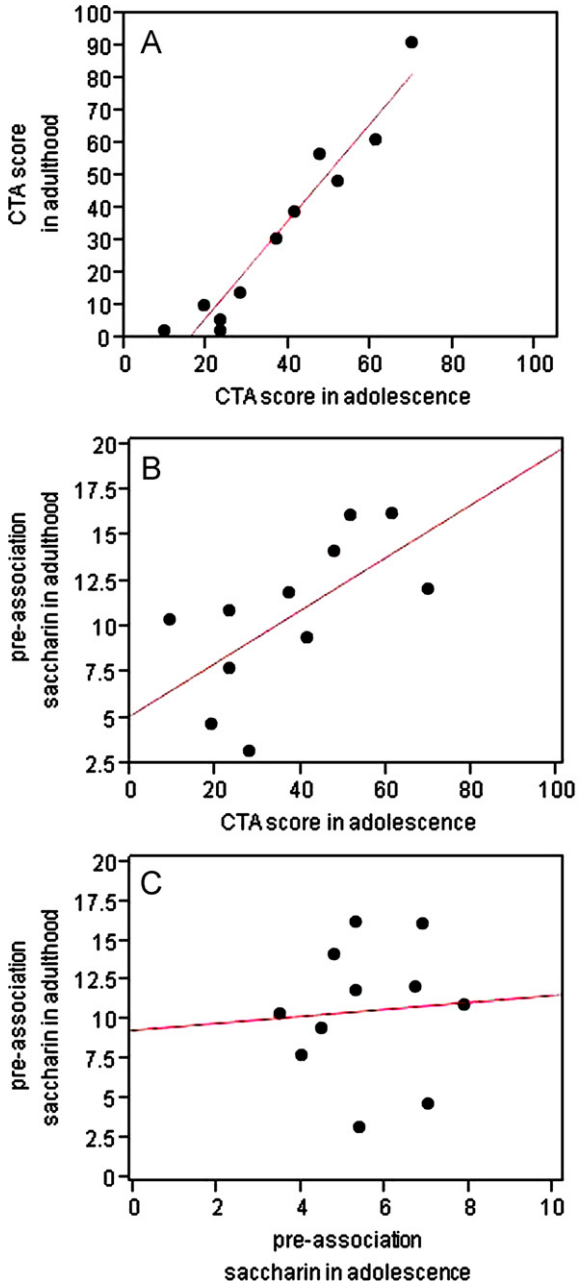

Fig. 1. Rats were tested in the CTA task at 28–33 days of age (adolescence) and then retrained and retested at 88–93 days of age (adulthood). (A) CTA score is consistent within individuals from adolescence into adulthood. By linear regression, $R^2 = 0.93$; $p < 0.0001$. (B) CTA score in adolescence is correlated with approach to saccharin in adulthood prior to re-pairing of saccharin and cocaine ($R^2 = 0.42$; $p = 0.03$). (C) Saccharin approach prior to association with cocaine is not consistent from adolescence into adulthood ($R^2 = 0.005$; $p = 0.83$).

The group average was also relatively stable. Comparing the group average when CTA is measured in adulthood vs. adolescence revealed no difference between the two ages (Adolescent scores: mean ± SEM = 37 ± 5%; Adult scores: 31 ± 8%; $p = 0.12$, RMANOVA). Thus, CTA score is a stable trait within individuals across these age groups.

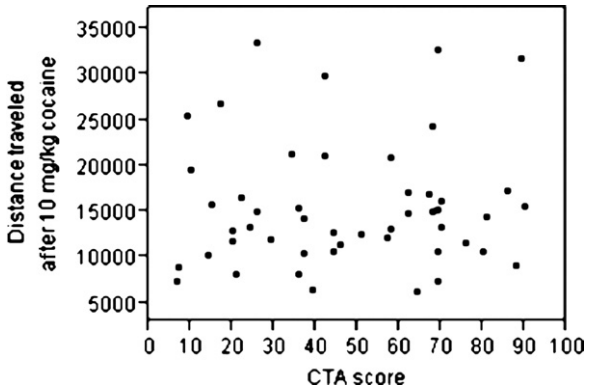

Fig. 2. CTA score is not correlated with cocaine-induced locomotion. Rats were tested in the conditioned taste aversion task at 28–33 days of age with assessment of cocaine-induced locomotion after the saccharin-drinking session. By linear regression, $R^2 = 0.02$, and $p = 0.36$.

Retention of the memory of CTA learned in adolescence partially accounts for the CTA score in adulthood. As shown in Fig. 1b, CTA score in adolescence is significantly correlated with saccharin intake prior to saccharin-cocaine pairing in adulthood ($R^2 = 0.42$, $p = 0.03$). In contrast, the rats' innate approach to saccharin does not seem to account for variation in approach to saccharin in adulthood or their CTA scores in adulthood. There is no correlation between pre-association saccharin consumption in adolescence and pre-association saccharin consumption in adulthood ($R^2 = 0.005$, $p = 0.8$, and Fig. 1c), and also no correlation between pre-association saccharin in adolescence and CTA score in adulthood ($R^2 = 0.03$, $p = 0.6$, data not shown).

3.2. Variation in CTA is not related to variation in locomotor effects of cocaine

As illustrated in Fig. 2, when CTA and cocaine-induced locomotion were assessed concurrently, there was no correlation between these two measures ($R^2 = 0.02$; $p = 0.36$). This indicates that differences in CTA scores are not paralleled by variations in rats' sensitivity to the locomotor effects of cocaine. Locomotion in response to a novel environment was also assessed after the water-drinking day, and was also not correlated with CTA score ($R^2 = 0.04$; $p = 0.24$), data not shown.

3.3. Strength of motivational effects is related to blood and brain levels via a quadratic function

As shown in Fig. 3, the squared value of the CTA score is related to the blood and brain levels of cocaine measured one week later (CTA score^2 vs. blood cocaine levels: $R^2 = 0.39$, $p = 0.005$; CTA score^2 vs. brain cocaine levels: $R^2 = 0.42$, $p = 0.003$). Rats that exhibited either high or low CTA scores also had high levels of cocaine in both blood and brain. Rats with intermediate CTA scores, reflecting weak aversions/preferences, exhibited low levels of cocaine in blood and brain. The linear correlation between CTA score and blood or brain cocaine levels was not statistically significant (CTA score vs. brain cocaine

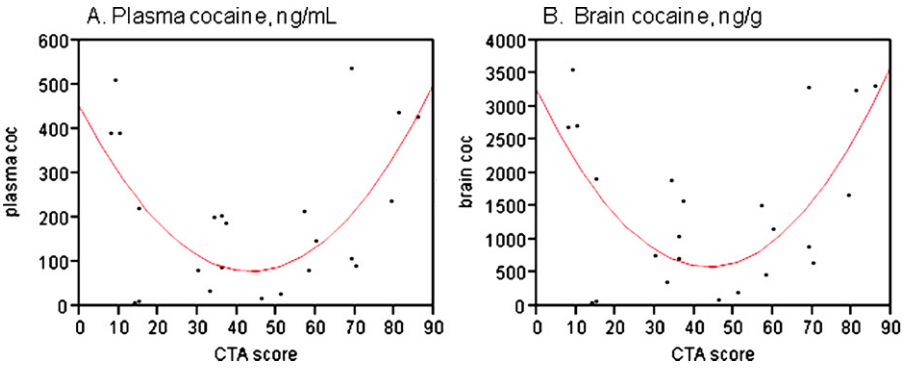

Fig. 3. Blood and brain cocaine levels are a quadratic function of CTA score. Rats were tested in CTA in response to 10 mg/kg cocaine at 28–33 days of age. One week later, they were injected intraperitoneally with cocaine and sacrificed 30 min later for collection of trunk blood and brain tissue. Samples were analyzed by the Center for Human Toxicology, University of Utah. (A) By polynomial regression, plasma cocaine = 57.4 + 0.5(CTA score) + 0.19(CTA score-45)^2; $R^2 = 0.39$, and $p = 0.005$. (B) By polynomial regression, brain cocaine = 442 + 3.6(CTA score) + 1.4(CTA score)^2; $R^2 = 0.42$, and $p = 0.003$.

levels: $R^2 = 0.01$; $p = 0.7$; CTA score vs. blood cocaine levels: $R^2 = 0.01$; $p = 0.71$). High levels of cocaine in the brain are therefore associated with strong motivational effects, but the direction of those effects is not determined by pharmacologic availability.

4. Discussion

These results reflect two key findings. First, interindividual variation in sensitivity to the conditioned effects of cocaine is stable across development from adolescence into adulthood. Second, interindividual variation in these effects does not parallel the locomotor effects of cocaine. Taken together, these results suggest that each rat's innate balance of sensitivity to the rewarding and aversive motivational effects of cocaine is a stable trait which is likely mediated by a differing neural circuitry than the one that subserves locomotion.

We also observed a quadratic relationship between CTA score and levels of cocaine in the blood and brain. Rats that exhibited high levels of the drug exhibited either strong avoidance or strong approach to cocaine-paired saccharin. It will be interesting to pursue the question of what determines the directionality of the motivational effects in animals with high drug levels.

Based on the current study and previous observations from our lab involving ethanol CTA and ethanol consumption (Schramm-Sapyta et al., 2010), we would predict that the rats that most strongly approached the cocaine-paired saccharin (highest CTA scores) would also consume the most cocaine in a self-administration setting, while those that avoided cocaine-paired saccharin would also avoid cocaine itself. However, a number of reports (Grigson, 2008; Grigson and Freet, 2000; Grigson and Twining, 2002; Liu et al., 2009) interpret CTA scores differently. These authors describe avoidance of drug-paired saccharin as indicative of the rewarding effects of the addictive drug and of the drug's ability to devalue natural rewards. In other words, the rats avoid the drug-paired saccharin in anticipation of the greater reward (the drug) and because repeated pairings of the drug and natural reward have made the natural reward (saccharin) less desirable. Some important experimental differences exist between the methods used by these authors and our methods which influence our interpretation. Their rats were repeatedly given exposure to the flavored solution followed by self-administration of the drugs of abuse, whereas our rats were given a single opportunity to consume saccharin followed by experimenter-administered cocaine. Our version of the CTA task measured acute effects, whereas repeated exposures to the drug and conditioned tastant make their method more sensitive to developing changes in hedonic behavior.

Beyond simple experimental differences, a recent paper sheds light on the complexity of interpreting CTA data. Wheeler et al. demonstrated that with repeated days of saccharin-drug access pairing, rats performed more mouth movements which were indicative of aversion to the saccharin flavor (Wheeler et al., 2008). However, the rats that exhibit the greatest number of aversive mouth movements were also the animals which performed the self-administration behavior most ardently. Both behaviors (aversive mouth movements and increasing self-administration behavior) increased over repeated pairings. Therefore, the authors argue, the aversive behaviors could result from the daily experience of cocaine withdrawal.

The complexity of cocaine's motivational effects has also been demonstrated by a series of studies demonstrating that it can be simultaneously rewarding and aversive. In the same way that the rats in the Wheeler et al. study both performed aversive mouth movements and took cocaine, Ettenberg and Geist (1991,1993), Geist and Ettenberg (1990,1997) have shown that cocaine approach slows down with repeated exposure. In their runway model, rats receive intravenous cocaine after daily traversals of a long runway. With repeated training, the rats begin to exhibit reversals and hesitation to enter the cocaine-associated goal box. With repeated exposure, therefore, cocaine clearly elicits simultaneous approach and avoidance motivations. A similar observation has been reported with amphetamine (Wang et al., 2010). It remains to be determined whether CTA is a measure of reward or

aversion, but the current data demonstrate that within individuals, it is consistent from adolescence into adulthood.

Retention of the memory of the cocaine-saccharin association learned during adolescence may also play a role in the reduced aversion we observed in adulthood. The animals that remembered a positive association with saccharin continued to approach it in adulthood, both before and after it was re-paired with cocaine. However, retention of the memory does not fully account for the strong correlation between adolescent and adult CTA score, as evidenced by the fact that the correlation between CTA scores post-association at the two ages (Fig. 1a) is much stronger than the correlation between the CTA score in adolescence and the pre-association saccharin consumption in adulthood (Fig. 1b). The stronger association after repairing suggests that a consistency in interoceptive effects of cocaine strongly drives the approach to cocaine-paired saccharin.

The current findings differ slightly from our previous reports in which we have compared separate groups of adolescents and adults side-by-side. Those reports have shown that adolescent rats as a group exhibit reduced CTA compared to adults (Schramm-Sapyta et al., 2006, 2007, 2010). Our previous report with cocaine demonstrated adolescent CTA scores around 40%, similar to the current report, but adult scores around 15%, lower than the scores in the current report (31%) and indicative of stronger avoidance of cocaine-paired saccharin (Schramm-Sapyta et al., 2006). Thus, adult aversions are reduced in the current study compared to the previous study.

There are two likely explanations for this discrepancy between the current test–retest results and previous between-group comparisons: the pre-exposure effect and neophobia. The pre-exposure effect is the attenuation of conditioned aversion to a drug (the unconditioned stimulus) after previous exposure to it. This effect has been demonstrated for pre-exposure to morphine, ethanol, and THC (Diaz-Granados and Graham, 2007; Stewart and Eikelboom, 1978; Switzman et al., 1981; Ton and Amit, 1983), and appears to be stronger when the pre-exposure occurs during adolescence (Diaz-Granados and Graham, 2007). Our rats, which had received their "pre-exposure" to cocaine during the first CTA task in adolescence, exhibited a pre-exposure effect which weakened the second aversion, resulting in a higher CTA score. Neophobia to the conditioned stimulus, saccharin, also plays a significant role in CTA learning. One recent meta-analysis identifies the amygdala as being involved in the recognition of the saccharin taste as novel (Reilly and Bornovalova, 2005). Furthermore, amygdalo-cortical connections are immature in adolescence (Cunningham et al., 2002; Cunningham et al., 2008; Ernst et al., 2005; Eshel et al., 2007). Adult rats in our previous experiments accurately perceived saccharin as novel and more easily avoided it. Adolescents, perhaps due to their immature amygdalo-cortical. In the current experiment, however, the saccharin was not novel to the adults, which likely resulted in reduced taste aversion.

Taken together with these published observations, the current results suggest that adolescent exposure to cocaine may have the effect of reducing cocaine's aversive properties throughout life, particularly in the individuals who find in non-aversive in adolescence. This may indicate that adolescent exposure to cocaine could create lifelong vulnerability to the motivational effects of cocaine, particularly in those individuals who find it most rewarding. Of course, it is impossible to track the stability of a behavior without performing a test–retest experiment such as this one, and therefore impossible to know whether the animals which did not find the cocaine aversive in adulthood would have also found it non-aversive if they had been tested only in adulthood.

The current results also shed light on the basis of interindividual differences in CTA. Since our results show that interindividual differences in CTA are not correlated with interindividual differences in acute cocaine-stimulated locomotion, then brain regions that are involved in CTA and not involved in cocaine-induced locomotion should form the basis of these differences. The prefrontal cortex, hypothalamus, nucleus accumbens, and ventral tegmental area have all been implicated in the locomotor effects of cocaine (Iniguez et al., 2010; Khan and Shoaib, 1996; Levy et al., 2007), whereas the ventral pallidum, parabrachial nucleus, amygdala, insular cortex, supramammillary nucleus, and nucleus accumbens are implicated in various aspects of CTA (Yamamoto, 2007). The current results suggest that we should examine the amygdala, parabrachial nucleus, supramammilary nucleus, and ventral pallidum as the brain regions potentially underlying interindividual differences in CTA. The ability to manipulate these brain regions may facilitate manipulation of drug approach and avoidance behaviors.

In summary, the demonstration that CTA scores are consistent as rats mature from adolescence into adulthood opens the door for much additional research. It is now reasonable to examine how an adolescent rat's CTA score correlates with other cocaine-related behavior, particularly drug-seeking and self-administration. If the relative interindividual differences in this measure are stable across development, then early identification of vulnerable individuals can provide beneficial lifelong awareness of innate risk and opportunity for protective intervention.

Acknowledgements

The authors wish to thank Drs. David Moody, Jerdravee Thammavong, David Andrenyak and Wenfang Fang at the Center for Human Toxicology, University of Utah, for analysis of cocaine levels in samples. This work was supported by the US National Institutes of Health, DA 020729, to NLSS.

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